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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte
DAVID A. EDWARDS and JEFFREY S. HRKACH

Appeal 2007-1137[1]
Application 09/822,716
Technology Center 1600

Decided: February 24, 2009 [2]

Before TONI R. SCHEINER, DONALD E. ADAMS, and ERIC GRIMES, *Administrative Patent Judges*.

SCHEINER, *Administrative Patent Judge*.

DECISION ON APPEAL

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[1] The real party in interest is Advanced Inhalation Research, Inc.
[2] The two-month time period for filing an appeal or commencing a civil action, as recited in 37 C.F.R. § 1.304, begins to run from the decided date shown on this page of the decision. The time period does not run from the Mail Date (paper delivery) or Notification Date (electronic delivery).

This is an appeal under 35 U.S.C. § 134 involving claims 1-8, 10, 13-29, and 49-52. We have jurisdiction under 35 U.S.C. § 6(b).

STATEMENT OF THE CASE

"[M]any illnesses or conditions require administration of a constant or sustained level[ ] of a bioactive agent to provide an effective therapy" (Spec. 2: 3-4). "However, delivery of bioactive agents to the pulmonary system typically results in rapid release of the agent following administration" (*id.* at 2: 7-8). "[A] need exists for formulations suitable for inhalation . . . wherein the bioactive agent of the formulation is released in a sustained fashion into the systemic and/or local circulation" (*id.* at 2: 15-17).

The present invention "is based upon the unexpected discovery that complexation of a multivalent metal cation with a therapeutic, prophylactic or diagnostic agent carrying a negative, and therefore opposite charge to that of the cation, results in a sustained release profile of the agent upon pulmonary delivery" (*id.* at 2: 19-22).

Claim 1 is representative of the claimed subject matter:

1. A method of delivery to the pulmonary system comprising:
administering to the respiratory tract of a patient in need of treatment, prophylaxis or diagnosis an effective amount of a dry powder comprising:
a) a multivalent metal cation which is complexed with a therapeutic, prophylactic or diagnostic agent;
b) a pharmaceutically acceptable carrier; and
c) optionally, a multivalent metal cation-containing component
wherein, the dry powder is spray-dried and has a total amount of multivalent metal cation which is more than about 1% w/w of the total weight of the agent, a tap density of less than about 0.4 g/cm^3, a median geometric diameter of between about 5 micrometers and about 30 micrometers and an aerodynamic diameter of from about 1 to about 5 microns.

Claims 1-8, 10, 13-29, and 49-52 are pending and on appeal.[3] The Examiner rejected the claims as follows:

Claims 1-8, 10, 13-17, 21-26, 28, 49, 51, and 52 under 35 U.S.C. § 103(a) as unpatentable over Jensen (U.S. Patent 6,043,214, issued March 28, 2000) in view of Maa (U.S. Patent 6,284,282 B1, issued September 4, 2001);

Claims 1-8, 10, 13-17, 21-28, and 49-52 under 35 U.S.C. § 103(a) as unpatentable over Jensen in view of Weers (U.S. Patent 6,309,623 B1, issued October 30, 2001); and

Claims 18-20 and 29 under 35 U.S.C. § 103(a) as unpatentable over Jensen in view of the International Cosmetic Ingredient Dictionary and Handbook, Volume 2, 7th Edition (Ed. John A. Wenninger, The Cosmetic, Toiletry, and Fragrance Assn., Washington, D.C.) (1997) (the "Cosmetic Handbook").

We reverse.

THE ISSUE

The issue raised by this appeal is whether the Examiner has established that the prior art relied on discloses or suggests a dry powder, obtainable by spray drying, comprising a multivalent metal cation complexed with a therapeutic agent, wherein the powder has a tap density of less than about 0.4 g/cm^3, a median geometric diameter of between about 5 μm and about 30 μm and an aerodynamic diameter of from about 1 μm to about 5 μm.

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[3] The Examiner included claims 9, 11, 12, and 30-48 in one or more of the rejections in the Answer, but these claims were canceled by amendments filed May 24, 2004 and September 20, 2004.

FINDINGS OF FACT

FF1 According to the Specification, "complexation of a multivalent metal cation with a therapeutic, prophylactic or diagnostic agent carrying a negative, and therefore opposite charge to that of the cation, results in a sustained release profile of the agent upon pulmonary delivery" (Spec. 2: 19-22).

FF2 The Specification teaches that "the agent can be insulin and the multivalent metal cation can be zinc" (Spec. 7: 3-6).

FF3 In order to form a complex between insulin and the cation, the insulin is "mixed with the desired metal cation component in an aqueous buffer system (e.g. citrate, phosphate, acetate, etc.), the pH of the resultant solution then can be adjusted to . . . about pH 6.7. At this pH insulin molecules have a net negative charge . . . and complexation of the metal cation component to the insulin achieves a precipitate of the metal cation complexed insulin" (Spec. 8: 15-21). "[T]he solution containing the precipitated metal cation complexed biologically active agent is mixed with a solution of the pharmaceutically acceptable [phospholipid] carrier . . . [and] solvent is then removed from the resulting mixture . . . for example, [by] lyophilization, evaporation and spray drying. Spray drying . . . is a preferred method" (*id.* at 8: 23-29; 10: 5-6).

FF4 The Specification teaches that

> Particles which have a tap density of less than about 0.4 g/cm^3, median diameters of at least about 5 μm, and an aerodynamic diameter of between about 1 μm and about 5 μm . . . are more capable of escaping inertial and gravitational deposition in the oropharyngeal region, and are targeted to the airways or the deep lung. The use of larger, more porous

> particles is advantageous since they are able to aerosolize more efficiently than smaller, denser aerosol particles . . .

(Spec. 19: 13-18).

FF5 Appellants claim a method of delivering a therapeutic, prophylactic, or diagnostic agent to the pulmonary system of a patient by administering a dry powder comprising (a) the agent complexed with a multivalent metal cation, wherein the multivalent metal cation is more than about 1% w/w of the total weight of the agent and (b) a pharmaceutically acceptable carrier. Claim 1 requires that the powder

- is spray-dried;
- has a tap density of less than about 0.4 g/cm^3;
- has a median geometric diameter of between about 5 micrometers and about 30 micrometers;
- and has an aerodynamic diameter of from about 1 to about 5 microns.

(Claim 1.)

Jensen

FF6 Jensen discloses a process for preparing "a therapeutic powder formulation comprising particles composed of insulin" (Jensen, col. 2: 42-43), starting with a) an acidic aqueous solution of insulin, a penetration enhancer (e.g., surfactants including phospholipids and bile salts), and zinc (zinc chloride solution); b) adjusting the pH to 4.5 to 7.4; c) precipitating a product comprising insulin, enhancer and zinc; and d) removing the water in

a vacuumdryer after allowing the preparation to stand at rest for 16 hours (*id.* at col. 2, ll. 46-54; col. 3, ll. 1-3; Examples I-IV).

FF7 According to Jensen, the precipitates formed in step c) of the method are initially amorphous, but become crystalline upon standing in water, and "[t]he size of the individual crystals was determined to [be] 1μ-5μ" in all of the working examples (Jensen, Examples I-IV).

FF8 Jensen's process "results in a [crystalline] powder formulation of insulin and enhancer which elucidates a better stability profile [and better flow properties] than powders of essentially the same composition prepared by spray drying, freeze-drying, vacuum drying and open drying" (Jensen, col. 2, ll. 55-59, 66), which "have been described as mainly amorphous" (*id.* at. col. 1, ll. 59-60).

FF9 Jensen does not disclose the aerodynamic diameter or tap density of the particles in his dry powder formulation.

Maa

FF10 Maa teaches that "[t]he success of a dry powder inhalation product is based on the ease of powder dispersibility . . . Many physical characteristics affect the dispersibility of the powder, including . . . particle size/distribution, particle shape/morphology, and moisture content" (Maa, col. 4, ll. 1-7). In general, "diminishing the density of the particle may permit delivery of larger particle sizes into the deep lungs" (*id.* at col. 4, ll. 53-55). In other words, "a light (low density) particle having the same physical size . . . as a heavy (high density) particle . . . will have a smaller aerodynamic size than the heavy particle; therefore, light particles are [more]

likely to travel with air streamlines and reach in the deep lung" (*id.* at col. 4, ll. 42-47).

FF11 Maa discloses "spray freeze-dried formulations of therapeutic proteins [including insulin], that show good dispersibility and respirable properties, as well as good stability" (Maa, col. 3, ll. 54-56; col. 6, ll. 46).

FF12 Unlike Jensen's formulations, Maa's formulations are "substantially free of 'penetration enhancers'", i.e., surfactants) (Maa, col. 9, ll. 47-49).

FF13 According to Maa,

> Spray freeze drying is a process conceptually similar to spray drying, in that a homogeneous aqueous mixture of a therapeutic protein, termed herein the "pre-spray freeze dry formulation", is introduced via a nozzle . . . , spinning disk or an equivalent device into a cold fluid to atomize the solution to form fine droplets. . . . [but] [t]he cold fluid, either a liquid or a gas, is at a temperature below the freezing point of the aqueous solvent of the pre-spray freeze dry formulation. Spraying the formulation into the cold fluid results in the rapid freezing of the atomized droplets to form particles. The particles are collected, and then the solvent is removed, generally through sublimation (lyophilization) in a vacuum. . . . This produces a fine dry powder having particles of a specified size and characteristics . . .

(Maa, col. 5, ll. 8-28).

FF14 Maa's spray freeze dried powders are "characterized on the basis of a number of parameters, including, . . . the average particle size, the range of particle sizes, . . . the average particle density, and the mass median aerodynamic diameter (MMAD)" (Maa, col. 5, ll. 43-47). The particles preferably have "tap densities of less than about 0.4 g/cm^3" (*id.* at col. 6, ll. 8-9), an "average particle size rang[ing] from about 5 μm to about 30 μm"

(*id.* at col. 5, ll. 50-51), and "an aerodynamic mass median diameter of less than 6.8 μm" (*id.* at 5, ll. 61-62).

FF15 Maa compared the physical properties of spray dried (SD) and spray freeze dried (SFD) powders of rhDNAse and anti-IgE antibody, and found "a significant difference between SD and SFD" (Maa, col. 18, l. 46). Essentially, during spray drying, atomized particles shrink upon water removal, and the resultant dried particles have different shapes depending upon formulation and drying conditions. During spray freeze drying, the atomized particles maintain their shape and size upon water removal, and simply become more porous (*id.* at col. 18, ll. 46-55). Maa teaches that "[s]pray freeze-dried powders consistently outperformed spray-dried powders" (*id.* at col. 19, 21-22), and suggests that "the superior aerosol performance by the spray freeze-dried powder might be simply due to its smaller aerodynamic particle size despite its larger physical size" (*id.* at col. 19, ll. 53-56).

Weers

FF16 Weers describes "perforated microstructures" comprising "a powder of dry, hollow, porous microspherical shells" with a mean geometric particle size "preferably about 0.5-50 μm , more preferably 1-30 μm . . . less than 20 μm or less than 10 μm", especially approximately "1 to 10 μm in diameter, with shell thicknesses of approximately 0.1 μm to approximately 0.5 μm" (Weers, col. 13, ll. 35-50). The microstructures typically have a density of less than 0.5 g/cm^3, and a mean aerodynamic diameter of less than about 5 μm, or roughly three times smaller than their median geometric diameter (*id.* at col. 14, ll. 28-41).

FF17 The perforated microstructures are designed for administration by metered dose inhaler (MDI), which delivers an active agent in the form of a solution or dispersion (Weers, col. 1, ll. 39-42). The perforated microstructures are stabilized by suspending them in a fluid medium with approximately the same apparent density as the microstructures. In Weers' "homodispersion," the suspension medium infiltrates the microstructures, "substantially eliminating the attractive van der Waals forces" (Weers, col. 9, l. 41; col. 11, ll. 25-28), and allowing the suspension to be free-flowing even when the microstructures are closely packed (*id.* at col. 11, ll. 43-49).

FF18 "[T]he components of the microparticle matrix" are highly variable, and "are preferably selected, as much as possible given other considerations, to approximate the density of the suspension medium" (*id.* at col. 11, ll. 29-32). The perforated microstructures may comprise essentially 100% active agent, or may comprise "relatively high levels of surfactants (i.e., phospholipids)", i.e., anywhere between 1% and "essentially 100%" (Weers, col. 17, ll. 45-65). In addition, "the structural matrix defining the perforated microstructure optionally comprises synthetic or natural polymers . . . [e.g.] polylactides, polylactide-glycolides, cyclodextrins, . . . polyvinyl pyrrolidones, polysaccharides (dextrans, starches, chitin, chitosan, etc.), hyaluronic acid, proteins, (albumin, collagen, gelatin, etc.)" (*id.* at col. 18, ll. 10-19).

FF19 Weers' perforated microstructures may be formed by spray drying an emulsion formed from whatever components are to be included in the microstructures, additional surfactants, and an inflating or blowing agent (e.g., perfluorohexane, Freon, or carbon dioxide) which vaporizes during the

spray drying process, leaving behind hollow, porous microstructures (Weers, col. 21, l. 55 to col. 22, l. 11). Examples I-XVIII show that the physical and aerodynamic properties of Weers' perforated microstructures are highly variable depending on the base composition of the particles, the amount and type of surfactants incorporated, and the type of inflating agent used, etc.

PRINCIPLES OF LAW

"[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006). "[T]his analysis should be made explicit" and it "can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *KSR International Co., v. Teleflex Inc.*, 550 U.S. 398, ___, 127 S. Ct. 1727, 1741 (2007).

ANALYSIS

The present claims require a dry powder comprising a therapeutic agent-multivalent metal cation complex (an insulin-zinc complex, for example), obtained (or obtainable) by spray drying, with a specified tap density, geometric diameter, and aerodynamic diameter. The powder is delivered to the pulmonary system of a patient in need of treatment.

Jensen and Maa

The Examiner concluded that the invention of claims 1-8, 10, 13-17, 21-26, 28, 49, 51, and 52 is unpatentable over Jensen and Maa because one of skill in the art, "given the general teachings of a powder formulation of insulin of

Jensen" (Ans. 4), would have looked to other prior art references, such as Maa, "for specific particle characteristics" of "effective formulations for pulmonary delivery" (*id.*). Moreover, the Examiner asserts that "the instant claims are drawn to a method of delivery and not a method of making particles, thus the specific steps of preparation are not examined here and not given patentable weight" (*id.* at 7).

Appellants contend that the requirement that the product be spray dried cannot be ignored, "[w]here, as here, the evidence suggests that the process has a substantive impact on the product" (App. Br. 5). Appellants contend that there is no evidence that Jensen's crystalline powders have the tap density, geometric diameter, and aerodynamic diameter required by the claims, nor is there any reason one of skill in the art would expect to obtain a powder with the required physical properties by "mix[ing] and match[ing] components of the[ ] two very different processes" disclosed by Jensen and Maa (*id.* at 5).

As discussed above, Jensen describes a dry powder for delivery to the pulmonary system comprising insulin, penetration-enhancing surfactants, and zinc (FF6). However, Jensen's powder is not made by spray drying, and is not disclosed to have the various physical properties required by the claims (FF6, 7). Jensen mentions prior art spray dried powders "of essentially the same composition" (FF8), but the Examiner has not established that any of those spray dried powders have the various physical properties required by the claims. Moreover, Jensen's powders are crystalline, while the prior art spray dried powders are described as amorphous (FF7, 8). In addition, Jensen teaches that his crystalline powders

differ from spray dried powders in terms of stability and flow properties (FF8).

Maa, on the other hand, describes a dry powder comprising a protein (insulin, for example), which is not complexed with a multivalent metal cation, but which does meet the limitations of the claims with respect to tap density, median geometric diameter, and aerodynamic diameter (FF11, 14). However, Maa's powders are made by spray freeze drying, rather than spray drying, and Maa attributes the physical properties and "superior" performance of his powders to the spray freeze drying process (FF13, 15).

Given these facts, we agree with Appellants that the Examiner has not established that any of the powders disclosed by Jensen have the physical properties required by the claims. Moreover, even if one skilled in the art would have had a reason to use Maa's spray freeze dry process to prepare a powder from Jensen's starting composition, the Examiner has not established that the physical properties required by the claims would have been obtained, given the differences between Jensen's starting composition and Maa's starting composition (e.g., the presence of surfactants in Jensen's composition, versus the lack of surfactants in Maa's (FF6, 12)). Finally, both references disclose that protein-containing powders for inhalation therapy made by spray drying were known in the art, but both references indicate that such powders differ from powders made by Jensen's method or Maa's method, and the Examiner has not provided any rational basis for concluding that spray dried powders would have been expected to have the physical properties required by the claims.

Jensen and Weers

The Examiner concluded that the invention of claims 1-8, 10, 13-17, 21-28, and 49-52 is unpatentable over Jensen and Weers because one of skill in the art, "given the general teachings of a powder formulation of insulin of Jensen" (Ans. 5), would have looked to other prior art references, such as Weers, "for specific particle characteristics" of "effective formulations for pulmonary delivery" (*id.*). Again, the Examiner asserts that "the instant claims are drawn to a method of delivery and not a method of making particles, thus the specific steps of preparation are not examined here and not given patentable weight" (*id.* at 7).

As discussed above, Jensen is directed to making and administering dry, crystalline powders, while Weers is directed to a method of making and administering a "homodispersion" of perforated microstructures suspended in a fluid of approximately the same apparent density (FF17). The composition and physical properties of the microstructures are highly variable, but their composition complements, and is dependent on the composition and density of the suspension medium (FF18, 19).

We agree with Appellants that it would not have been obvious for one skilled in the art to have prepared Jensen's dry powders using Weers' method, given the differences in their objectives. Moreover, even if one skilled in the art would have had a reason to use Weers' process to prepare a powder from Jensen's starting composition, the Examiner has not established that the physical properties required by the claims would have been obtained, given the highly variable physical properties obtained with

Weers' method depending on the starting composition of the microstructures (FF19).

Jensen and the Cosmetic Handbook

The Examiner concluded that the invention of claims 18-20 and 29 is unpatentable over Jensen and the Cosmetic Handbook because the Cosmetic Handbook discloses that carboxylic acids "are well known pH adjusters in pharmaceutical and cosmetic formulations" and it would have been obvious to substitute a carboxylic acid for Jensen's hydrochloric acid "to perform a pH adjusting function" (Ans. 6).

Nevertheless, we agree with Appellants that the Cosmetic Handbook "does not provide what the Jensen and Weers [and Maa] references lack" (App. Br. 9-10).

CONCLUSIONS OF LAW

The Examiner has not established that the prior art relied on discloses or suggests a dry powder, obtainable by spray drying, comprising a multivalent metal cation complexed with a therapeutic agent, wherein the powder has a tap density of less than about 0.4 g/cm^3, a median geometric diameter of between about 5 μm and about 30 μm and an aerodynamic diameter of from about 1 μm to about 5 μm.

SUMMARY

The rejection of claims 1-8, 10, 13-17, 21-26, 28, 49, 51, and 52 under 35 U.S.C. § 103(a) as unpatentable over Jensen and Maa is reversed.

The rejection of claims 1-8, 10, 13-17, 21-28, and 49-52 under 35 U.S.C. § 103(a) as unpatentable over Jensen in view of Weers is reversed.

The rejection of claims 18-20, and 29 under 35 U.S.C. § 103(a) as unpatentable over Jensen in view of the Cosmetic Handbook is reversed.

REVERSED

Ssc:

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